REMARKS

Status of Claims

Claims 1-9, 14, 16-26, 32, 50-51, and 60 are pending. Claims 1 and 32 are amended. Applicants reserve the right to pursue any canceled subject matter in one or more continuing applications.

Support for Amendments

Claims 1 and 32 are amended to specify that the recited limitation of mean particle size of 30-250 microns refers to the gelatin particles and not to the composition as a whole. Support for the size of the gelatin particles can be found in the application as filed, for example from page 6, line 24 through page 7, line 15.

No new matter is introduced.

Interview Summary

Applicants thank Examiners Tsay and Monshipouri for the courtesy of an in-person interview on March 16, 2010, with Applicants' representatives Jonathan D. Ball, Michael Willis, Jesper Levin Aamand, Marielle Dejligbjerg, and Janni Pedersen (see Interview Summary with a Notification Date of March 24, 2010). The cited references Ferdman, Yamamoto, Silver, and Yannas were discussed. Claims 1 and 34 were discussed. However, claim 34 and all claims dependent from claim 34 are cancelled upon entry of this paper. Therefore, Applicants respectfully request withdrawal of the rejection of claim 34 and claims dependent from claim 34 as being moot. Further arguments directed to the pending claims are presented below.

Claim Rejections

<u>35 U.S.C. § 112, first paragraph</u>

The Office Action rejects claims 1-9, 14, 16-26, 32, 50-51, and 60 under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. The Office Action indicates that this is a "new matter" rejection. Applicants respectfully traverse the

rejection. However, the Office Action indicates that there is support for a composition comprising gelatin powder, wherein said gelatin powder has a particle size of 30-250 microns, and hyaluronic acid. See Office Action, p. 3, lines 2-4. As the claims are amended accordingly, Applicants respectfully request withdrawal of the rejection.

35 U.S.C. § 103(a)

The Office Action rejects **claims 1-7, 14, 16-22, 25-26, 50-51, and 60** under 35 U.S.C. § 103(a) as being unpatentable in view of Ferdman (US Patent No. 5,951,531) combined with Yamamoto (US Publication No. 2001/0008636) and Silver (US Patent No. 5,196,185).

Claims 8-9, 34, 52-59, and 61 are rejected under 35 U.S.C. § 103(a) as being unpatentable in view of Ferdman (US Patent No. 5,951,531) combined with Yamamoto (US Publication No. 2001/0008636) and Silver (US Patent No. 5,196,185) and further in view of "knowledge in the art." See Office Action, p. 7, lines 13-14.

Claim 32 is rejected under 35 U.S.C. § 103(a) as being unpatentable in view of Ferdman (US Patent No. 5,951,531) combined with Yamamoto (US Publication No. 2001/0008636) and Silver (US Patent No. 5,196,185). See Office Action, p. 9, lines 6-18.

Dependent **claims 23-24** are rejected under 35 U.S.C. § 103(a) as being unpatentable in view of Ferdman (US Patent No. 5,951,531) combined with Yamamoto (US Publication No. 2001/0008636) and Silver (US Patent No. 5,196,185) as evidenced by Epstein (US Patent No. 6,045,570). See Office Action, p. 10, lines 1-19.

Applicants respectfully traverse the rejection of all of the claims for at least the reasons that (i) the cited references, either alone or in combination, fail to teach or suggest all of the claimed elements; (ii) the Office Action fails to provide a motivation for combining the cited references with a reasonable expectation of success because the references are not properly combinable; and (iii) and the specification provides evidence of the criticality of a claimed range. Additional reasons are provided below as applied to specific claims.

Claims 1-7, 14, 16-22, 25-26, 50-51, and 60

Claim 1 is directed to a powder delivery system containing a chamber storing a haemostatic composition comprising dry gelatin powder having a mean particle size in the range of 30-250 μm and hyaluronic acid, said chamber having at least one discharge opening sized for distributing said composition.

Dependent claims 2-7, 14, 16-22, 25-26, 50-51, and 60 include at least all of the features of claim 1. All of the above claims require a dry gelatin powder in a particle size in the range of 30-250 μm and hyaluronic acid.

Ferdman teaches an apparatus and a method for applying a particulate haemostatic agent, said apparatus comprising a haemostatic agent and a continuous gas source. The gas and the haemostatic agent are mixed in the apparatus and sprayed onto living tissue. Ferdman does not disclose a particle size for the haemostatic composition, or the incorporation of hyaluronic acid into the composition to be sprayed.

The newly cited **Yamamoto** reference relates to microcapsules comprising gelatin and HA for use as surgical adhesives. The mechanical effects of the surgical adhesives as taught by Yamamoto include wound closure or tissue bonding as an alternative to traditional sutures (i.e., a "glue" function), and a barrier function to isolate the wound from the surrounding environment. Regarding the biological functions of the surgical adhesive, Yamamoto teaches only a "tissue ingrowth" feature, and the gelatin and HA are only used by Yamamoto as an encapsulating shell material because of their biodegradable and adhesive properties, as explained in paragraph [0014] of the reference. Yamamoto does not teach or suggest the use of the composition as a haemostatic agent.

Furthermore, Yamamoto teaches that the microcapsules comprising gelatin and HA are delivered as an aqueous slurry. See paragraph [0034], and Example 1, wherein Yamamoto teaches gelatin and HA microcapsules consisting of 6 parts gelatin, 1 part hyaluronic acid (HA), 100 parts water and 25 parts mineral oil in an aqueous slurry. The composition taught by Yamamoto is thus not a dry and sprayable composition, as the composition of Yamamoto consists of only 5.3% dry matter (gelatin and HA) and 94.7% liquid (water and mineral oil).

Silver teaches compositions of particulate collagen for use in wound dressings with a range of particle sizes. Silver further teaches that HA can be added to promote tissue ingrowth:

> Hyaluronic acid in the collagen matrix encourages cellular infiltration into the pores and channels of the matrix.

Silver, col. 6, l. 2-4. There is no teaching or suggestion in Silver that HA, with the property of promoting tissue ingrowth, would be beneficial in a haemostatic composition. Moreover, Silver does not teach gelatin in powdered compositions, but rather teaches the use of gelatin as a carrier in gel form. See col. 3, lines 19-25. Furthermore, Silver teaches that the particulate collagen is mixed with a low molecular weight alcohol at a collagen to liquid ratio of 1:5 to 1:50 to form a collagen dispersion (see col. 2, lines 49 to 53 and lines 60 to 63). Thus, the composition of Silver is not dry as it contains from 80 to 98% liquid and from 2 to 20% collagen, and Silver fails to teach compositions of a haemostatic powder comprising gelatin and hyaluronic acid.

None of the cited references (Ferdman, Yamamoto, and Silver) teach or disclose dry gelatin powder having a mean particle size in the range of 30-250 μm. For example, the preferred size of collagen particles taught by Silver is 5-15 μm (col. 2, l. 35-38 of Silver), which is below the size range of the present invention of 30-250 μm, and is collagen rather than gelatin according to the instant claims. Silver does not teach gelatin, so one of ordinary skill in the art would not look to the teachings of Silver for the motivation to use gelatin particles of 30-250μm. For at least this reason alone, the rejection should be withdrawn.

Moreover, the Office Action fails to provide a motivation for combining the cited references with a reasonable expectation of success because the references are not properly combinable. According to the Examiner, the motivation to modify the teachings of Ferdman by adding hyaluronic acid to the gelatin composition is provided by Silver, which allegedly teaches that hyaluronic acid can promote tissue ingrowth, and by Yamamoto, which allegedly teaches that hyaluronic acid can be used with gelatin to make microcapsules.

However, an effect on tissue ingrowth cannot be equated with a haemostatic effect according to the instant claims. Tissue ingrowth relates to wound closure mechanisms and to the ability of the tissue cells surrounding a wound to proliferate and migrate, thus leading to wound closure, while a haemostatic effect relates to enhancing the ability of blood to coagulate and thus

stop bleeding. In other words, the two properties relate to different technical effects and are not necessarily desirable at the same time when treating a wound. Specifically, a haemostatic effect is desirable in acute wound treatment to stop bleeding, while tissue ingrowth is desirable in the later stage treatment of a wound to close up the wound with minimal scarring.

As such, there is no motivation to combine the tissue ingrowth compositions of Yamamoto and Silver with the haemostatic compositions of Ferdman, as the combination would likely defeat the purpose of each reference. The Office Action fails to provide any basis for predicting that a composition having an effect on tissue ingrowth is also haemostatic and vice versa, or that the tissue ingrowth properties of Yamamoto and Silver are desirable in the haemostatic compositions of Ferdman. Moreover, neither Yamamoto nor Silver teach a dry powder composition suitable for spraying. Specifically, the composition of Yamamoto contains almost 95% liquid, while the collagen-HA composition of Silver contains 80-98% liquid. Thus, the compositions taught by Yamamoto and Silver are not suitable to be combined with Ferdman, which is directed to a dry powder composition with a haemostatic effect for use in a powder delivery system. Absent hindsight reconstruction of Applicant's own invention, one of ordinary skill in the art at the time of the invention simply could not have envisioned combining Yamamoto or Silver with Ferdman.

Finally, Applicants have provided evidence of the criticality of the claimed mean particle size range of 30-250 μm for the dry gelatin powder according to the instant claims:

> As will be acknowledged by the skilled person, a powder with a very small particle size, such as a mean particle size of less than about 10 μm, will give cause technical problems due to poor flowability. Further will a very small particle size give problems with dust while applying the powder. Therefore, the mean particle size of the powder must therefore be a compromise between particles of a mean particle size of at least 10 μm. On the other hand, the particles should not be too large, i.e. the particles should have a mean particle size of less than 250 μm.

See Specification, p. 6, line 36 through p. 7, line 3.

The instant description also provides comparative experiments showing that the powder of the invention of a certain particle size is superior over prior art products with a larger particle

size such as Surgifoam®. See Example 6 of the present invention for data on improved wetability of a powder with a mean particle size of about 80 μm (Example 2, page 23, line 22), which is within the claimed range of the present invention (30-250 μm) compared to Surgifoam®. The particle size of Surgifoam® is disclosed in the present application on page 7, lines 20-24 and is about 350 μm. The top table on page 27 clearly shows that the wetability and thus the capacity for absorbing liquid is significantly improved with the powder of the present invention having a particle size within the claimed range compared to Surgifoam®. The two tables at the bottom of page 27 show that the powder of the present invention absorbs saline faster than Surgifoam® and that the absorbance capacity is higher. Therefore, the claimed gelatin powder mean particle range of 30-250 μm is associated with a critical range yielding significantly improved absorption properties.

Claims 8-9

The Office Action rejects claims 8-9, 34, 52-59, and 61. However, claims 34, 52-59, and 61 are canceled upon entry of this paper. Therefore, Applicants request that the rejection of claims 34-52-59, and 61 be withdrawn as moot. The following comments are directed to pending claims 8-9.

Ferdman teaches an apparatus and a method for applying a particulate haemostatic agent, said apparatus comprising a haemostatic agent and a continuous gas source. The gas and the haemostatic agent are mixed in the apparatus and sprayed onto living tissue. The Office Action concedes that Ferdman does not teach "an attachment to the nozzle of the powder delivery system." See Office Action, page 7, lines 13-16.

The Office Action relies on a "general search of the prior art" which allegedly "reveals powder delivery systems with different types of nozzles and structural extensions," (Office Action, page 8, lines 1-3), yet the Office Action fails to cite this prior art to make it of record. Applicants respectfully submit that it is improper for the Office Action to rely on uncited art or secret art in making a rejection, and for at least this reason, the Office Action fails to make a prima facie case of obviousness.

Applicants refer to the above arguments with respect to the deficiencies of the combination of Ferdman, Yamamoto, and Silver with respect to claim 1, from which claims 8-9 depend. Claim 1 requires a dry gelatin powder in a particle size in the range of 30-250 μm and hyaluronic acid.

Further, for the teachings of Ferdman to be combinable with other teachings in the art there must be a motivation to do so. Applicant respectfully submits that Ferdman provides no motivation for attaching any kind of structure to the discharge opening, let alone a protective structure with a well-defined functionality as described in the application as filed.

The Office Action compares the nozzle of a delivery system with the outlet of a vacuum cleaner to which various structures can be attached. However, the analogy fails because, while an attachment to a vacuum cleaner outlet may result in accessibility to narrow spaces, there is no protective function in a vacuum cleaner attachment. Indeed, the whole purpose of a vacuum cleaner attachment is to get into as close contact with a surface as possible, which is the complete opposite of the protective structure of the present invention. The protective structure of the present invention is configured at the end of the discharge opening in order to, at least to some extent, isolate the discharge opening from the surroundings. The protective structure confers a decreased risk of clogging of the nozzle as the nozzle cannot be brought into direct contact with a surface, such as a bleeding wound. This is evident from the specification:

> A special distance protective structure is illustrated in Fig. 4. The embodiment shown comprises a ring (12) supported by legs (13), so the discharge opening (4) of the extended nozzle cannot abut a surface. Alternatively, the protective structure may be a skirt (not shown) attached to the discharge opening (4), said skirt extending in front of the discharge opening (4) of the extended nozzle.

Specification, page 21, lines 7-11.

For at least the same reasons as for claims 1-7, 14, 16-22, 25-26, 50-51, and 60, and the additional reasons that the Office Action relies on uncited art and a false analogy, Applicants request withdrawal of the rejection of claims 8-9.

Claim 32

Independent claim 32 is directed to a method for promoting haemostasis in a patient in need thereof, said method comprising spraying a haemostatic powder composition comprising gelatin having a mean particle size in the range of 30-250 μm and hyaluronic acid, wherein said powder is dry, onto at least a portion of an area where bleeding occurs.

The Office Action attributes a teaching of spraying haemostatic compositions onto wounds to Silver. See Office Action, page 9, lines 14-15. This is incorrect, as Silver provides no teaching that the taught compositions are haemostatic.

For at least the same reasons as for claims 1-7, 14, 16-22, 25-26, 50-51, and 60, and the additional reasons that the Office Action incorrectly summarizes the teachings of Silver, Applicants request withdrawal of the rejection of claim 32.

Claims 23-24

Dependent claims 23-24 are directed to compositions, wherein said compositions further comprises a coagulation factor, such as thrombin. The Office Action relies on the teachings of Epstein with respect to thrombin as an agent to be mixed with collagen powder in order to form a biological sealant composition. See Office Action, p. 10, lines 1-16. However, Epstein fails to remedy the deficiencies of Ferdman, Yamamoto, and Silver with respect to haemostatic composition comprising a dry gelatin powder in a mean particle size in the range of 30-250 μm and hyaluronic acid.

For at least the same reasons as for claims 1-7, 14, 16-22, 25-26, 50-51, and 60, and the additional reasons that Epstein fails to remedy the deficiencies of the previous three references, Applicants request withdrawal of the rejection of claims 23-24.

Unexpected Results

In further support of the non-obviousness of the present invention, Applicants direct the Examiner to Yannas (US Patent No. 4,280,954; previously cited and considered by the Examiner

as evidenced by the signed form attached to the May 20, 2009 Office Action). Yannas teaches composite materials of collagen and a mucopolysaccharide, which are said to have anti-coagulant properties. Specifically, Yannas is concerned with "blood compatible" composite materials:

> As used herein, "blood-compatible" means that a material compares favorably with human blood vessels in three regards: (1) tendency no to cause platelet aggregation; (2) tendency not to cause clotting of red blood cells; and preferably, (3) tendency not to interfere with the competence of healthy blood to clot.

Yannas, col. 10, l. 40-46. In contrast, the instant compositions are pro-coagulant and comprise gelatin. Therefore, the present invention is directed to solving a different technical problem than Yannas. Specifically, Yannas explicitly teaches away from using HA in a haemostatic composition:

> [H]yaluronic acid composites have not been found to cause platelet aggregation.[1]

Yannas, col. 11, l. 8-9. Yannas further teaches:

> Reaction with mucopolysaccharides appears to suppress essentially the entire procoagulant activity and thrombogenic nature of native collagen.[2]

See Yannas, col. 3, lines 41-44. Moreover, Examples 12 and 13 of Yannas show that the HA-collagen composites fail to exhibit significant differences in whole blood clotting time (WBCT) compared to collagen itself. These data demonstrate that collagen-HA is comparable to collagen alone in reducing whole blood clotting time under the conditions specified by Yannas, and therefore would not suggest the use of this combination in a pro-clotting combination. Indeed, the data presented by Yannas highlight the surprising discovery that compositions comprising gelatin and HA according to the present invention possess a pro-coagulant effect, let alone a synergistic pro-coagulant effect. This effect would in no way be expected from the teachings of Yannas. Thus, the Yannas reference demonstrates that there is unpredictability in the art with regards to the technical effect of combining collagen or gelatin with a mucopolysaccharide such as hyaluronic acid.

[1] Platelet aggregation is required in the sequence of events leading to the formation of a blood clot.

[2] While collagen and gelatin are different, gelatin can be made by partial hydrolysis of collagen, and both have haemostatic properties.

Applicants further direct the Examiner's attention to Moller (US Publication 2007/0009578; pending as US 10/562,831; co-owned), which provides evidence of a synergistic effect. Sponges were prepared according to Example 1:

> A HA gel (2% (w/v)) was prepared from *Streptococcus Equi* sp hyaluronic acid sodium salt (Biochemika) with a molecular weight of 1,500-1,800 kDa. The gel was added to freshly foamed gelatine (16.7% (w/v)). Immediately after addition of HA, the mixture was whirled at high velocity to avoid clogging of the gelatine. In order to avoid an inhomogeneous mixture, the temperature should not be below room temperature. After mixing, the mixture was poured into trays or placed on finely perforated teflon sheets, followed by air drying at approximately 30° C. and 10% relative humidity for about 16 hours. Sponges prepared this way typically had a HA content of about 25-50% (w/w).

(See US 2007/0009578, paragraph [0181]). Following preparation, sponges were evaluated for the reduction of bleeding intensity in a porcine spleen model, with evaluation of the following compositions:

> A sponge of gelatine with and without HA (S4 vs. S1)
>
> A sponge of oxidised cellulose with and without HA (S9 vs. S8)
>
> A powder of gelatine with and without HA (S3 vs. S2)
>
> A sponge of gelatine with thrombin (S7)
>
> The S1 sponge was a commercially available gelatine sponge Spongostan®.
>
> The S4 sponge was prepared as described above and then subsequently treated with dry heat by placing it in a paper-bag in an oven at 150° C. for 90 min.
>
> The S7 sponge was a Spongostan® sponge, which was further soaked in a 1000 U/mL thrombin-solution.
>
> The S8 sponge was a commercially available sponge of oxidised cellulose, called Surgicel®.
>
> The S9 sponge was prepared by wetting the commercially available sponge Surgicel® in a gel of HA until the concentration of HA in the sponge was 10% w/w. The sponge with HA was then subsequently freeze-dried.
>
> The powder without HA (S2) was prepared by milling a Spongostan® sponge and just before application mixing the powder with saline to obtain a paste.

> The powder with HA (S3) was prepared similarly by milling a Spongostan® sponge and then subsequently mixing the powder obtained by said milling with HA powder and then just before application adding saline to this mixture to obtain a paste.

(See US 2007/0009578, paragraphs [0197] through [0207]). The haemostatic efficacy of the samples was evaluated by the following method:

> An incision was made into the spleen and the intensity of the resulting bleeding was evaluated on a scale ranging from 0-5. Subsequently, the sample in question was applied to the incision and at predetermined intervals, the sample was lifted from the incision and the intensity of the bleeding was evaluated before the sample was reapplied. Powder samples and oxidised cellulose samples were not lifted from the incision which is very likely to affect the reduction in the bleeding intensity also for the compositions without HA. The bleeding intensity was in those cases evaluated by the amount of blood leaking through the samples. Each experiment was terminated after 7 minutes if haemostasis (0 on the scale) had not occurred before. 7 repetitions (distributed onto all four pigs) were performed for each type of sample, except for the reference samples for which 3 repetitions were performed on each pig, i.e. 12 repetitions in total.

(See US 2007/0009578, paragraph [0209]). The bleeding intensity reduction was calculated for each experiment as the difference between the evaluated bleeding intensities at the start and at the end of the experiment. The resulting averages of these numbers are shown in the table below:

Sample	Average bleeding intensity reduction	Lifting of the composition from the incision for evaluation of the bleeding intensity
S1: Gelatine sponge (Spongostan®), heated at 150°C for 180 min	0.82	Yes
S4: Gelatine sponge with 30% w/w HA (Biochemika), heated at 150°C for 90 min	4.29	Yes
S7: Gelatine sponge (Spongostan®) with thrombin	3.00	Yes
S2: Gelatine powder irradiated (e-beam) with 15 kGy	2.86	No

S3: Gelatine powder with 10 % w/w HA (HTL) and irradiated (e-beam) with 15 kGy	3.67	No
S8: Sponge of oxidised cellulose (Surgicel®)	2.71	No
S9: Sponge of oxidised cellulose (Surgicel®) with 10 % w/w HA (HTL)	3.29	No

(See US 2007/0009578, paragraph [0211]). The results show that a gelatin sponge, a gelatin powder and a sponge of oxidized cellulose with hyaluronic acid (HA) reduce the bleeding intensity more than the same sponges and powder without HA (S4 vs. Sl, S3 vs. S2 and S9 vs. S8). Specifically, in comparing S4 vs. S1, it can be seen that a gelatin sponge with 30% HA thus reduces bleeding 5.23 times better than a gelatin sponge with hyaluronic acid (see above table). Furthermore, the results also show that a gelatin sponge with HA results in a larger reduction in the bleeding intensity than a gelatin sponge with thrombin (S4 vs. S7). The data show the improved haemostatic effect of gelatin and HA, which would not have been predicted from the teaching of Yannas.

In conclusion, when considering all of the prior art, which includes the teachings of Yannas, it would not have been obvious to one of ordinary skill in the art to combine Ferdman with Yamamoto and Silver, and even when combined, the cited references fail to teach all of the claimed features. Moreover, as Yannas clearly suggests that a combination of gelatin and HA would have an anti-coagulant effect, the data provided above is clear evidence of an unexpected result.

For at least the reasons discussed above, the cited references fail to render the instant claims obvious. Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants respectfully submit that the instant application is in condition for allowance. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided.

AUTHORIZATION

The Commissioner is hereby authorized to charge any fees which may be required for this paper, or credit any overpayment to Deposit Account No. **50-3732**, Order No. **13323.105002**. Furthermore, in the event that an extension of time is required, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to the above-noted Deposit Account No. **50-3732** and Order No. **13323.105002**.

Respectfully submitted,
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